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Podcast 33: Partial D Phenotype and Hemolytic Disease in Babies

Tony Casina:

Welcome to QuidelOrtho Science BYTES. We're proud to sponsor this podcast as a continuing commitment to transform the power of diagnostics into a healthier future for all. Today our topic is can partial RHD phenotype cause hemolytic disease of the fetus and a newborn.

I am Tony Casina and today I am joined by Dr. Genghis Lopez. Dr. Lopez is a senior scientist at the Australian Red Cross Lifeblood in Brisbane, Australia. Dr. Lopez received his PhD degree from Griffith University in Australia. At Lifeblood, he worked at the platelet and granulocyte reference laboratory and red cell reference laboratory and is now part of the transfusion science research team that investigates complex red cell blood group variants. He has published several papers in Vox Sanguinis and Transfusion journals, reporting novel red cell antigens, novel blood types, and red cell antibodies, including several associated with hemolytic transfusion reactions or hemolytic disease of the fetus and a newborn.

Thank you so very much for joining us today, Dr. Lopez.

Dr. Lopez:

Happy to be here, Tony. Thank you.

Tony Casina:

Okay, let's get started with our first question. Can you give us sort of a biology of HDN and what causes it?

Dr. Lopez:

Surely. So hemolytic disease of the fetus and newborn or HDFN is a condition that occurs when maternal red cell IgG antibodies cross the placenta. Then it might, so it's cognate antigen targeting fetal red cells for destruction and in some cases suppress fetal erythropoiesis. These mechanisms can lead to fetal anemia.

So prenatal tests for fetal anemia can be diagnosed by using a doppler ultrasound that measures the middle cerebral artery peak systolic velocity. After birth, the risk of neonatal hyperbilirubinemia increases significantly, so the newborn may appear pale and jaundiced, and if left untreated, bilirubin can damage the brain, which can be life-threatening or it can lead to lifelong disability. So laboratory diagnosis for HDFN include positive DAT and detection of red cell antibodies in the mother's sample or elements in the fetal red cells or baby's red cells. In HDN, due to anti-D, large number of reticulocytes and nucleated red cells is expected on blood films.

Tony Casina:

Okay, thank you. So which type of hemolytic disease of the newborn and fetus is considered the most severe occurrence of HDN?

Dr. Lopez:

Many red cell antibodies, including anti-Kell and anti-c, have been reported to cause severe HDFN.

However, antibodies to the RhD antigen are the most frequent cause of moderate to severe HDFN in Caucasians. While it's less frequent in the Asian population, most common cause of HDN is anti-D in the Indian and Chinese populations.

Tony Casina:

Thank you. Can a first child develop hemolytic disease of the newborn?

Dr. Lopez:

Generally no. First pregnancies in RhD negative mothers who carry an RhD positive fetus are safe because the mother has not yet formed anti-D. So RhD negative pregnant women who are exposed to D-positive fetal red cells upon delivery can form anti-D. So when the mother is alloimmunized, succeeding pregnancies are at risk where the fetuses are actually positive.

However, there is an exception. Say if the mother has already formed anti-D, for example, due to transfusion of D+ red cells, then her pregnancy can be affected by HDFN if the fetus is D-positive.

Tony Casina:

Okay, thank you. This next question relates to your publications. There were two that caught my attention because they relate specifically to the topic of discussion today. In the first one published in 2017, you and collaborators describe anti-D and a mother who is hemizygous for the variant RHD-DNB gene that is associated with hemolytic disease of the fetus and newborn. And in the second from 2019, there is a description of a severe case of hemolytic disease occurring in a baby who has inherited a novel RHD allele associated with a partial RhD positive phenotype.

So my question is what do we know about RhD variants and hemolytic disease of the fetus and newborn and its occurrence?

Dr. Lopez:

Yeah, so RhD variants, as the name suggests, is any variation in the normal expression of the RhD antigen on red cells, and this could arise from nucleotide sequence changes in the RHD gene. RhD variants are generally classified as quantitative or qualitative. An example of a quantitative variant are your weak Ds, your weak D type one, two, and three. Generally weak D red cells have reduced quantity of RhD protein expressed on their membrane, but still express the full D epitope profile.

The second group, the qualitative variants, lack some or many D epitopes and are called partial D. So partial D can arise from single-nucleotide polymorphisms or due to multiple SNPs or could even be formation of hybrid genes where a section of the RHD gene was replaced by RHCE, resulting in amino acid changes that are located in the extracellular region of the RhD protein. Generally red cells with a partial D phenotype are D-positive, but the individuals can make anti-D following exposure to D-positive red cells.

So as you mentioned earlier, Tony, yeah, we previously reported two HDFN cases due to anti-D and associated with a partial D. The main difference is that in case one, the alloimmunized mother has a partial D phenotype, and in case two the fetus carry an RhD variant associated with a partial D B3 type.

Tony Casina:

Okay, thank you for that clarification on that. The next question that we have is related to knowing that variants present is dependent on demographics. Are there any statistics on prevalence you can share with us regarding RhD partial situations causing hemolytic disease?

Dr. Lopez:

So, regarding the prevalence and type of partial D, this varies within population groups. For example, in the African population, DAU, the D3, and DAR have been reported as the most common partial Ds. In the Asian populations, DFR was reported as most common in the Western Indian population, and RHD-weak partial 15 and D6 type three were reported as most common in the Chinese population. In the Caucasian population, most common partial Ds are your D6, your D7 and DNB, and they've been associated with moderate to severe HDFN.

Tony Casina:

Yes, one of my first experiences very early on in my career was with a D3 individual that had a baby that was quite severely affected by HDN, so yeah, I see where demographics play a role in understanding these individuals who are partial Ds and plays a role in what to look for in these individuals.

Dr. Lopez:

Yes.

Tony Casina:

Okay, thank you. The next question is really one that will close us out. What would your advice be to the transfusion medicine laboratories that manage maternal and neonatal populations in order to contribute to better clinical outcomes overall for them?

Dr. Lopez:

Several countries have their own guidelines on how to manage pregnant women with red cell antibodies. Generally, these guidelines recommend that as part of antenatal care, pregnant women have their blood group and antibody status determined, and once it is determined, if the mother is RhD negative and antibody screen negative, they're offered antenatal anti-D prophylaxis at 28 and 34 weeks gestation and postnatal within 72 hours if the baby is D-positive.

In pregnancies where the mother is D-neg and has formed anti-D, these cases should be referred to a maternal fetal medicine specialist for clinical monitoring and management. If non-invasive fetal genotyping is available, determine the RHD gene status of the fetus, and if fetus is predicted to be RhD positive, monitoring for fetal anemia is important. If fetal anemia is detected, intrauterine transfusions may be required. So these recommendations, if followed, can help prevent hemolytic disease of the fetus and newborn.

Tony Casina:

Great, thank you. Dr. Lopez, I really want to thank you for taking the time with us today and giving us

your experiences and insights on this fascinating topic. It's been a pleasure to talk with you, Dr. Lopez, and again, thank you so much for your time today on this podcast.

Dr. Lopez:

Thank you very much, Tony.

Tony Casina:

You're welcome.

I hope you all have enjoyed this podcast episode about can partial RhD phenotypes cause hemolytic disease of the fetus and a newborn and the challenges that they present to the transfusion service. Make sure to review the sections within the podcast description for any reading materials that we've suggested. Based on today's podcast, I'll leave you with our pop quiz. What type of HDN can be quite severe based on the blood group antibody specificity involved? You can always go back and listen again.

Thank you for listening and please subscribe to QuidelOrtho Science BYTES, brought to you by QuidelOrtho Corporation, where we are transforming the power of diagnostics into a healthier future for all. Take care. Stay healthy and safe.